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AUTHOR: Greenblatt MS, Bennett WP, Hollstein M, Harris CC

ADDRESS: Laboratory of Human Carcinogenesis, National Cancer Institute, Bethesda, Maryland 20892

TITLE: **Mutations in the p53 tumor suppressor gene: clues to cancer etiology and molecular pathogenesis**

SOURCE: Cancer Res; 54(18):4855-78 1994

ABSTRACT:

The p53 tumor suppressor gene is commonly mutated in human cancer and the spectrum of these mutations provides clues to the etiology and molecular pathogenesis of neoplastic disease. Alterations in p53 may have diagnostic, prognostic and therapeutic implications. There is an overview of the origins of mutation, presenting major types of base transitions and transversions observed and error rates for DNA replication. The spectrum of mutations (mostly single base substitutions) seen in housekeeping genes in vitro and in animal models are listed in a table; p53 mutations are less common in murine primary tumors than in human cancers. 2567 human p53 mutations were identified; results appear in a large table and 2 figures. The highest frequencies of p53 mutations reported for human cancers are: lung 56%, colon 50%, esophagus 45%, ovary, pancreas and skin, 44%, stomach 41%, head and neck 37%, bladder 34%, prostate 30%, breast, endometrium, and mesothelioma 22%. Analytical methods include DNA sequencing, immunohistochemistry, gel electrophoresis, and polymerase chain reaction techniques. Exons 5-8 account for 87%, exon 4, 8%, and exon 10, 4% of the mutations. Strand bias is characteristic of environmental carcinogens, e.g., 91% of G:C to T:A transitions in human lung cancer affect nontranscribed strand, indicating the importance of DNA repair in mutation specificity of cancer-related genes. The next section covers the functions and properties of p53 and its protein, its conformation, and the relationship of mutations to evolutionary conservation of p53 (missense mutations account for 79% of those in this region). Topics discussed are: p53 is only one of several pathways whose disruption leads to neoplastic transformation; the timing of p53 mutations in human carcinogenesis which may be either early or late in different cancers; the relationship of p53 mutations to more advanced stage and grade, metastatic phenotypes and angiogenesis; in vitro features of immortalization and neoplastic transformation; carcinogens and specific organ carcinogenesis, a

neoplastic transformation; carcinogens and specific organ carcinogenesis, a large subsection dealing with **skin cancer** and uv light, aflatoxin and hepatitis in liver **cancer**, tobacco-induced cancers, radiation and **cancer**, human papillomavirus in cervical **cancer**, endogenous sources of **mutation** such as 5-methylcytosine deamination, and mutational spectrum differences among populations, which stresses findings in China, Japan, and Taiwan. The apparently greater aggressiveness of tumors with **p53** mutations requires further study. (288 Refs.)

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L3 ANSWER 27 OF 32 MEDLINE
ACCESSION NUMBER: 95096498 MEDLINE
DOCUMENT NUMBER: 95096498 PubMed ID: 7798610
TITLE: Genetic alterations in non-**melanoma skin cancer**.
AUTHOR: Rees J
CORPORATE SOURCE: University Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne, U.K.
SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1994 Dec) 103 (6) 747-50. Ref: 49
Journal code: 0426720. ISSN: 0022-202X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
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LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950215
Last Updated on STN: 19950215
Entered Medline: 19950124

AB Non-**melanoma skin cancer** is common and offers unrivaled opportunities to relate genetic changes to clinical and biologic behavior. Recent technical advances in molecular biology render genetic analysis of even the smallest **skin cancers** possible. In this **review** I will discuss the role of **p53** gene in skin carcinogenesis, the relation between **p53** immunostaining and **p53** mutation, and recent evidence for the involvement of putative tumor suppressor genes both on chromosome 9 and other chromosomes in non-**melanoma skin cancer**

L3 ANSWER 25 OF 32 MEDLINE
ACCESSION NUMBER: 96259918 MEDLINE
DOCUMENT NUMBER: 96259918 PubMed ID: 8710788
TITLE: [Tumor suppressor gene **p53**. Theoretical principles and their significance for pathology]. Das Tumorsuppressorgen **p53**. Die theoretischen Grundlagen und ihre Bedeutung fur die Pathologie.
AUTHOR: Poremba C; Bankfalvi A; Dockhorn-Dworniczak B
CORPORATE SOURCE: Gerhard-Domagk-Institut fur Pathologie, Westfalische Wilhelms-Universitat, Munster.
SOURCE: PATHOLOGE, (1996 May) 17 (3) 181-8. Ref: 62
Journal code: 8006541. ISSN: 0172-8113.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
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Entered Medline: 19960906

AB Mutations of the **p53** tumor-suppressor gene are the most common genetic alterations in human cancer, found in approximately 50% of all tumors. The importance of **p53** in human cancer attracts attention in molecular studies dealing with the pathogenesis, diagnosis and prognosis in tumor pathology. This **review** summarizes the current understanding of **p53** both on the genetic and protein level. Frequency and spectrum of somatic **p53** mutations in the carcinogenesis of breast cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma, squamous-cell carcinoma of the skin and malignant **melanoma** are discussed including our own investigations and studies published in the literature.

L3 ANSWER 3 OF 32 MEDLINE
ACCESSION NUMBER: 2003105503 MEDLINE
DOCUMENT NUMBER: 22505454 PubMed ID: 12619107
TITLE: TP53 mutations in human **skin cancers**.
AUTHOR: Giglia-Mari Giuseppina; Sarasin Alain
CORPORATE SOURCE: Laboratory of Genetic Instability and Cancer, UPR 2169-CNRS, Villejuif, France.
SOURCE: HUMAN MUTATION, (2003 Mar) 21 (3) 217-28. Ref: 60
Journal code: 9215429. ISSN: 1098-1004.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
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LANGUAGE: English
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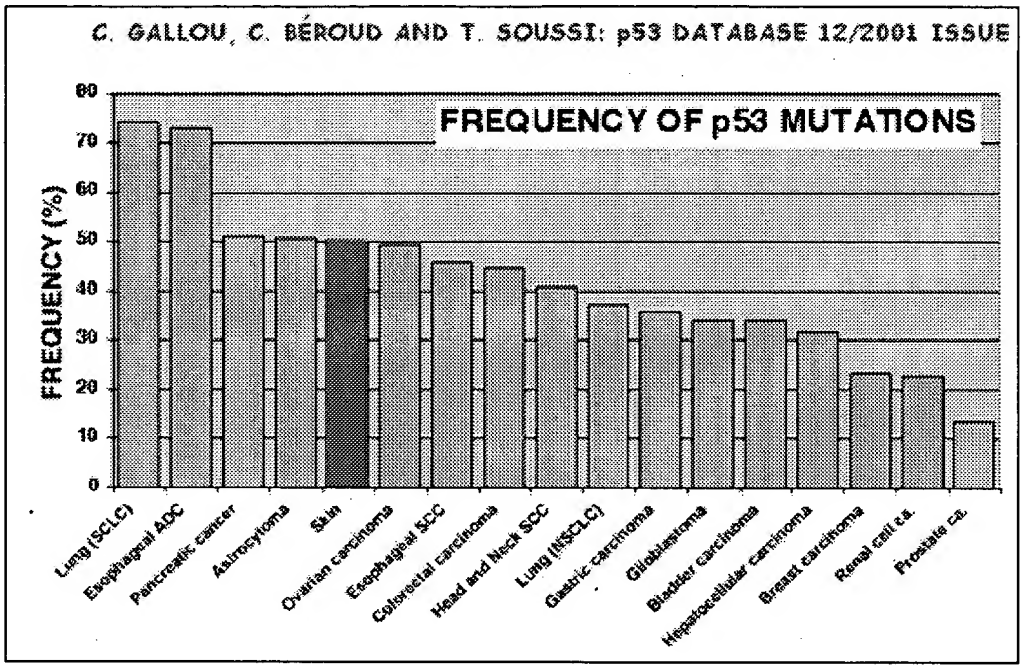
OTHER SOURCE: OMIM-191170
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030306
Last Updated on STN: 20030325
Entered Medline: 20030324

AB The **p53** gene (TP53) is mutated in numerous human cancers. We have used it as a molecular target to characterize the induction of mutations in human **skin cancers**. About 50% of all **skin cancers** in normal individuals exhibit **p53** mutations. This frequency rises to 90% in **skin cancers** of patients with the DNA-repair deficiency known as xeroderma pigmentosum (XP). These mutations are characterized by a specific signature, attributed to the ultraviolet uvB part of the solar spectrum. In this **review**, we will describe different **p53** mutation spectra, in relation to the various histopathological types of **skin cancers** such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant **melanoma** as well as to the DNA repair efficiency of the patients. In particular, different mutational hot spots are found among the various spectra. We have tried to elucidate them in terms of induced DNA lesion hot spots, as well as speed of local nucleotide excision repair (NER) or sequence effects. The molecular analysis of these mutagenic characteristics should help in the understanding of the origin of human **skin cancers** in the general population.

p53 IN SKIN CANCER



FREQUENCY OF p53 MUTATIONS IN SKIN CANCER

Basal cell carcinoma is the most common form of **skin cancer**. The second most common type of **skin** malignancy is squamous cell carcinoma. Although these 2 types of **skin cancer** are the most common of all malignancies, they account for less than 0.1% of patient deaths due to **cancer**. Both of these types of **skin cancer** are more likely to occur in individuals of light complexion who have had significant exposure to sunlight, and both types of **skin** cancers are more common in the southern latitudes of the Northern hemisphere. The overall cure rate for both types of **skin cancer** is directly related to the stage of the disease and the type of treatment employed. However, since neither basal cell carcinoma nor squamous cell carcinoma of the **skin** are reportable diseases, precise 5-year cure rates are not known. Although basal cell carcinoma and squamous cell

carcinoma are by far the most frequent types of skin tumors, the skin can also be the site of a large variety of malignant neoplasms. These other types of malignant disease include malignant melanoma, cutaneous T-cell lymphomas (mycosis fungoides), Kaposi's sarcoma, extramammary Paget's disease, apocrine carcinoma of the skin, and metastatic malignancies from various primary sites

Basal cell carcinoma and squamous cell carcinoma are both of epithelial origin. They are usually diagnosed on the basis of routine histopathology. Squamous cell carcinoma is graded 1 to 4 based on the proportion of differentiating cells present, the degree of atypicality of tumor cells, and the depth of tumor penetration. Apocrine carcinomas, which are rare, are associated with an indolent course and usually arise in the axilla.

Basal cell carcinoma

Basal cell carcinoma is at least 3 times more common than squamous cell carcinoma in nonimmunocompromised patients. It usually occurs on sun exposed areas of skin, and the nose is the most frequent site. Although there are many different clinical presentations for basal cell carcinoma, the most characteristic type is the asymptomatic nodular or nodular ulcerative lesion that is elevated from the surrounding skin and has a pearly quality and contains telangiectatic vessels. It is recognized that basal cell carcinoma has a tendency to be locally destructive. High-risk areas for tumor recurrence include the central face (periorbital region, eyelids, nasolabial fold, nose-cheek angle), postauricular region, pinna, ear canal, forehead, and scalp. A specific subtype of basal cell carcinoma is the morphea-form type. It typically appears as a scar-like, firm plaque and because of indistinct clinical tumor margins, it is difficult to treat adequately with traditional treatments.

Squamous cell carcinoma

Squamous cell tumors also tend to occur on sun-exposed portions of the skin such as the ears, lower lip, and dorsa of the hand. However, squamous cell carcinomas that arise in areas of non-sun-exposed skin or that originate de novo on areas of sun-exposed skin are prognostically worse since they have a greater tendency to metastasize. Chronic sun damage, sites of prior burns, arsenic exposure, chronic cutaneous inflammation as seen in long standing skin ulcers, and sites of previous x-ray therapy are predisposed to the development of squamous cell carcinoma.

Actinic keratosis

Actinic keratoses are potential precursors of squamous cell carcinoma. These typical red

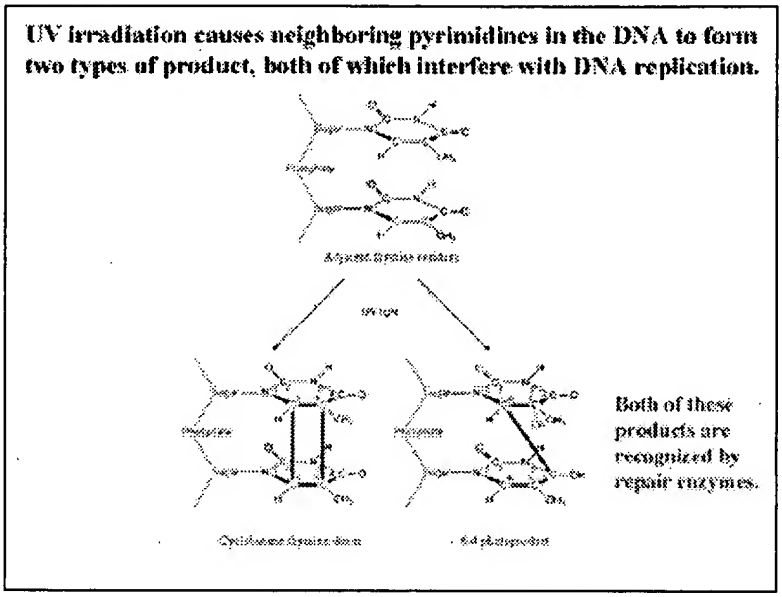
scaly patches usually arise on areas of chronically sun-exposed skin, and are likely to be found on the face and dorsal aspects of the hand. Although the vast majority of actinic keratoses do not become squamous cell carcinomas, it is thought that as many as 5% of actinic keratoses will evolve into this locally invasive carcinoma. Due to this premalignant potential, the destruction of actinic keratoses is advocated.

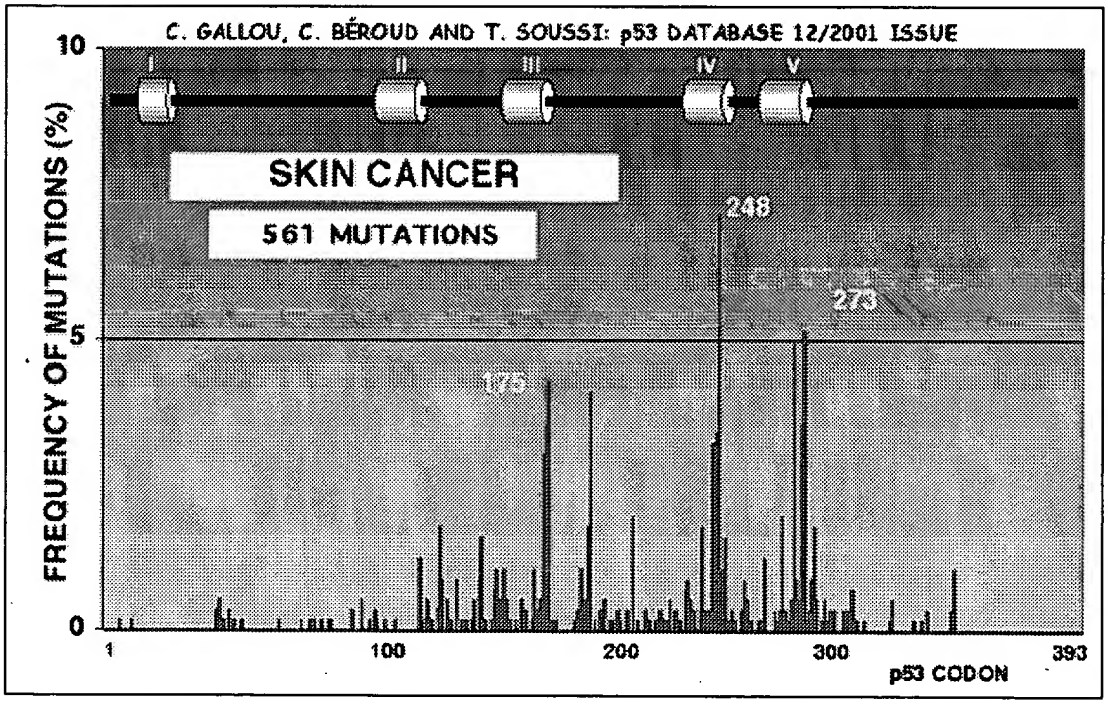
UV radiation-induced mutations have been studied in various animal models. The majority of the mutations are found to be located at dipyrimidine sites (i.e. (T-T, C-C, C-T or T-C) and correspond to a C to T transition. More than 20% correspond to tandem mutations involving the two adjacent nucleotides of the dipyrimidine sites (C-C to T-T).

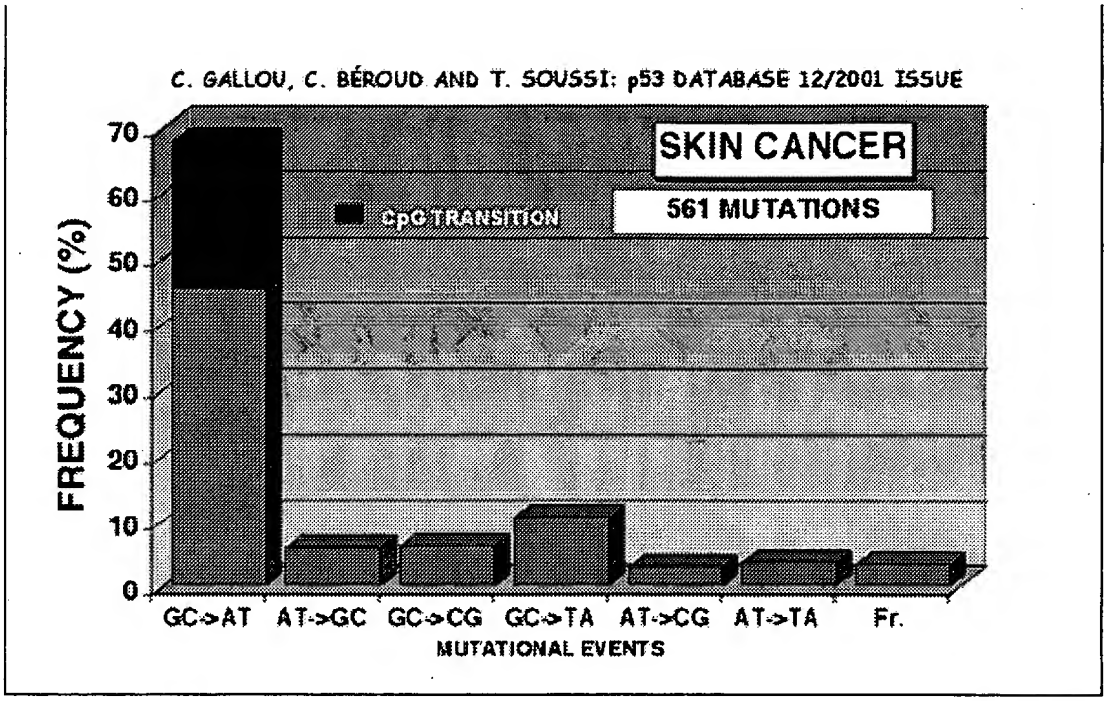
Several human genetic syndromes are associated with DNA repair deficiency. Among them, xeroderma pigmentosum (XP) is an autosomal, recessively inherited disease. Patients with XP show clinical and cellular hypersensitivity to UV radiation, resulting in a very high incidence of skin cancer. In these subjects, the median age of onset of skin cancer is 8 years, nearly 50 years younger than in the general population.

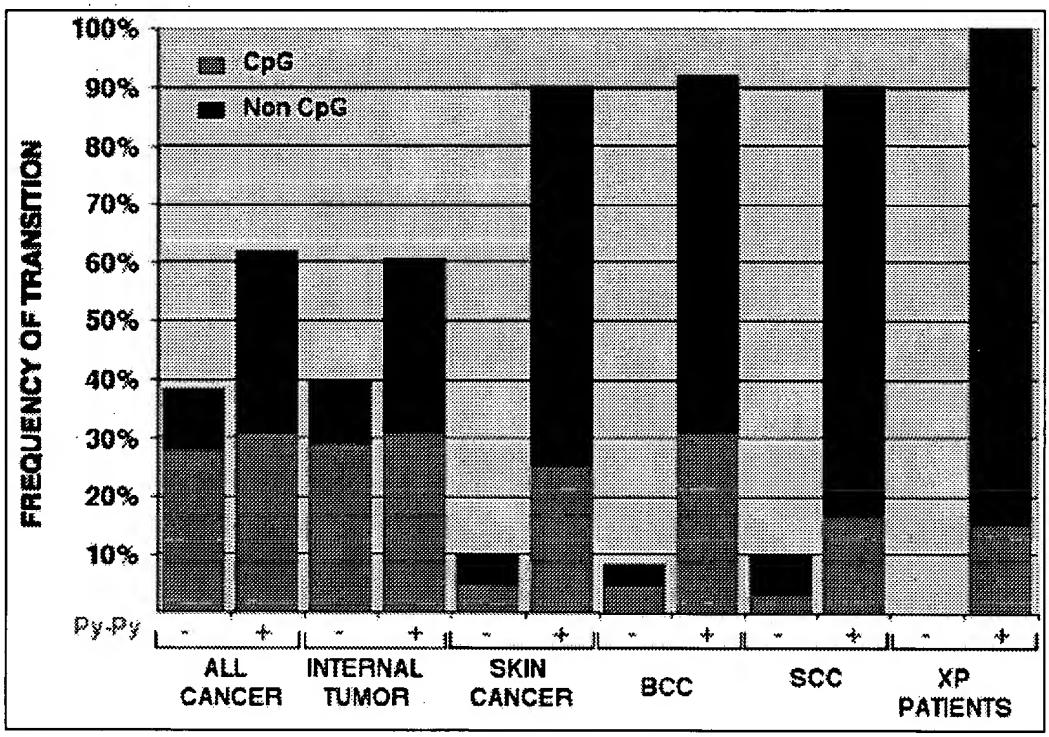
Brash et al. showed that, in skin spinocellular cancer, C ---> T mutations predominate in pyrimidine dimers. It is well known that ultraviolet radiation, an etiological agent of most skin cancers, acts directly on these dimers. A particular characteristic of the action of UV radiation is the change in the bases CC ---> TT, observed in Brash's series but also in other skin cancer series such as basocellular cancers (Rady et al. 1992). In patients with genetic DNA repair deficiencies, such as xeroderma pigmentosum (XP), the phenotype is much more marked. All mutations found in skin cancers are located on the pyrimidine dimers and 55 % are tandem mutations CC ---> TT (Dumaz et al. 1994). This type of mutation is only very rarely found in internal cancers (less than 1 %). In skin cancers from XP patients, more than 95 % of the mutations are located on the noncoding strand of the p53 gene, while in other skin tumors and in internal cancers, no special trends are observed. This result therefore suggests that there is preferential repair of the coding strand, which has been confirmed by Toranaletti and Pfeifer, who showed that the repair rate of pyrimidine dimers in the p53 gene is highly variable, with an especially low rate in the codons that are often mutated in skin cancer. Such p53 mutations seem to be very early events as they can be found both in precancerous lesions such as actinic keratosis (Ziegler et al. 1994) and in normal skin exposed to UV (Jonason et al. 1996). Recent work have demonstrated that human epidermal cancer and accompanying precursors have identical p53 mutations different from p53 mutations in adjacent areas of clonally expanded non-neoplastic keratinocytes (Ponten et al. 1997; Ren et al. 1997; Ren et al. 1996; Ren et al. 1997; Ren et al. 1996).

These results taken together (predominance of CC -> TT lesions on the non coding strand) were experimentally confirmed in animals carrying UV-induced tumors (Dumaz et al. 1997; Kress et al. 1992).



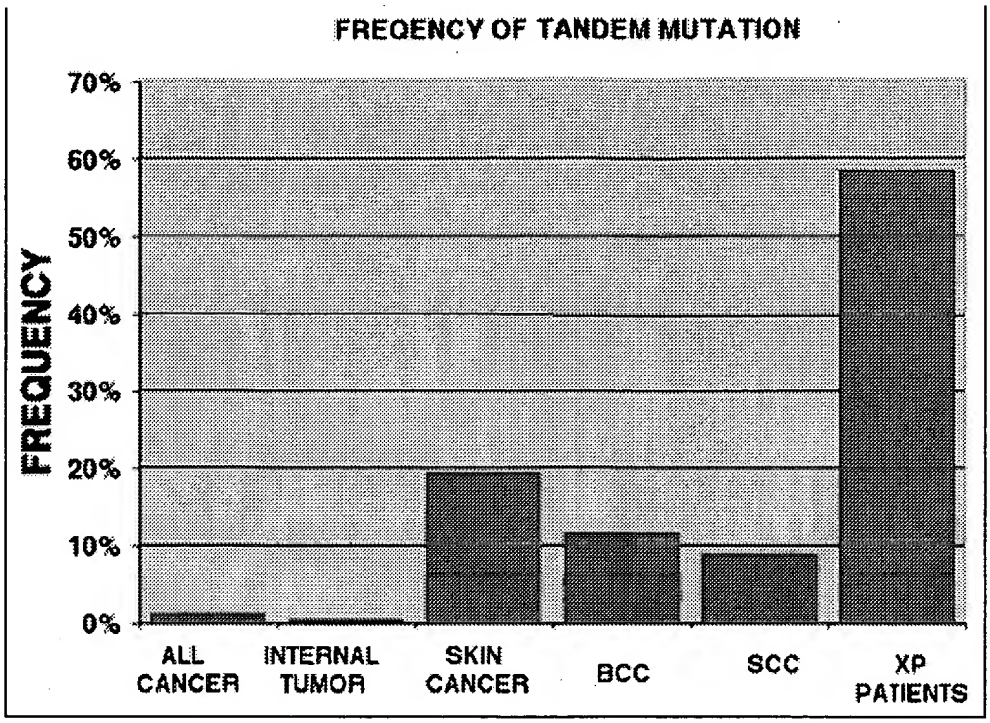






Transition at Py-Py site in Skin cancer

BCC: basal cell carcinoma; SCC: squamous cell carcinoma of the skin: XP: xeroderma pigmentosum patients.



Tandem mutation in Skin cancer

BCC: basal cell carcinoma; SCC: squamous cell carcinoma of the skin: XP: xeroderma pigmentosum patients.

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Short report

p53 mutations implicate sunlight in post-transplant skin cancer irrespective of human papillomarivus status

Jane M McGregor[1], Ron JM Berkhout[2], Magdalena Rozycka[3], Jan ter Schegget[2], Jan N Bouwes Bavinck[4], Louise Brooks[5] and Tim Crook[3,a]

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Abstract

Mutations in p53 were detected in 11/23 (48%) of non melanoma skin cancers in renal allograft recipients and in 5/8 (63%) of

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sporadic tumours from immune competent patients. 9/12 (75%) of mutations in transplant patients and all 5 mutations in non transplant tumours were consistent with damage caused by ultraviolet (u.v.) irradiation. DNA sequences, predominantly of the epidermodysplasia verruciformis (EV) subgroup, were detected in 9/23 (39%) of transplant tumours and in 2/8 (25%) of eight non-transplant tumours. There was no relationship between HPV status and p53 mutation, HPV DNA being present in 5/16 (31%) of tumours with p53 mutation and 6/15 (40%) of tumours lacking p53 mutation. These data are consistent with an important role for sunlight in the development of post-transplant skin cancer, and with limited functional data suggesting that E6 proteins of the cutaneous and EV-related papillomaviruses do not target p53 for ubiquitin-mediated degradation.

Keywords

non-melanoma skin; transplantation; p53 gene; human papillomavirus

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MINI-REVIEW ARTICLE

A model for UV-induction of skin cancer

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The cellular and molecular events that contribute to the development of UV-induced skin cancer is a complex process involving at least two distinct pathways that interact or converge to cause skin cancer (Figure 1). One pathway involves the action of UV on target cells (keratinocytes) for neoplastic transformation, and the other involves the effects of UV on the host's immune system [1]. There is evidence to indicate that UV-induced DNA damage plays an important role in both pathways.

In the normal human epidermis, cells are constantly turning over, about once a month. During this period, stem cells in the basal layer undergo cell division, and the keratinocytes differentiate into squamous cells producing keratin and other proteins, and finally desquamate. Chronic exposure to sunlight causes damage to the skin including erythema, edema, hyperplasia, formation of sunburn cells, photoaging, suppression of the immune system and skin cancer. Some of the molecular events that occur in cells following UV exposure are DNA damage, induction of p53 and p53-regulated proteins, cell cycle arrest, DNA repair, and apoptosis. UV-induced DNA damage causes an elevation of p53 expression and p53 protein is translocated to the nucleus to regulate its downstream genes. Among these genes, $p^{21waf1/Cip1}$ expression is induced to mediate cell cycle arrest at G1-S phase to allow the repair of DNA damage. UV can also induce apoptosis to order cells containing damaged DNA to self-destruct. It has been shown that UV-induced apoptosis is p53-dependent [2]. Interestingly, we have recently demonstrated that p53 may up-regulate *bax* and down-regulate Bcl-2 protein resulting in apoptosis [3] and that Fas/Fas-ligand pathway is essential for UV-induced apoptosis [4].

Following chronic UV exposure, errors associated with DNA repair and/or replication can result into mutations in the *p53* gene, especially C→T or CC→TT transitions, considered as UV-molecular signature. The *p53* mutation in keratinocytes is probably an initiating event in UV skin carcinogenesis [5]. Because cells containing *p53* mutations are relatively more resistant to UV-induced apoptosis, they can acquire a growth advantage. It is likely that the mutated cells expand preferentially in a clonal fashion at the expense of the normal surrounding keratinocytes, that commit massive suicide by apoptosis, leading to the appearance of p53 mutated clones in the epidermis [5–7]. Chronic exposure to sunlight may cause mutations in the other *p53* allele and/or other unknown gene(s). Thus, another tumor suppressor gene known as *patched* (*ptc*) has been implicated in the development of basal cell carcinoma (BCC) [8, 9]. The human *ptc* gene was found to colocalize with the map location of nevoid basal cell carcinoma syndrome (NBCCS) on chromosome 9 at 9q22.3. NBCCS, also called basal cell nexus syndrome or Gorlin's syndrome, is a rare autosomal dominant disorder characterized by multiple BCC that appear at a young age on sun-exposed areas of the skin. Studies of NBCCS patients have shown that they have both genomic and sporadic mutations in the *ptc* gene, suggesting that these mutations are the ultimate cause of this disease. Sporadic *ptc* mutations have been found in BCC from otherwise normal individuals, some of which are UV-signature, either C→T or CC→TT changes. However, *ptc*

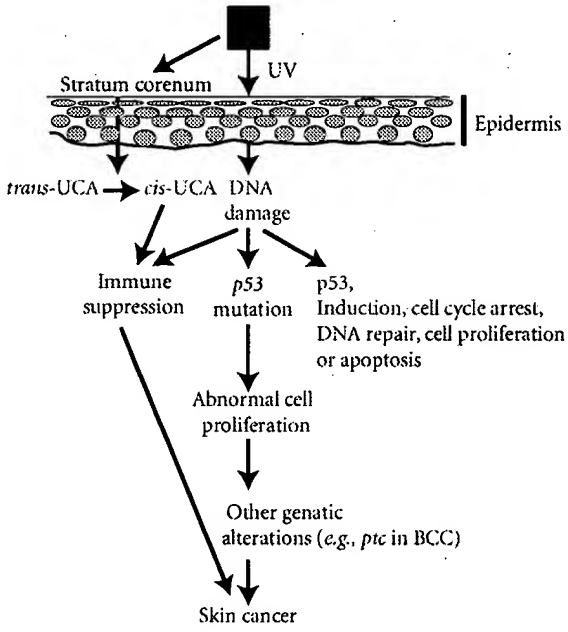

FIGURE 1: Pathways involved in skin cancer development.

mutations have not been reported in SCC. Nonetheless, these results suggest that genetic alterations in the *ptc* gene may also play a role in the development of BCC [9].

In addition, UV radiation causes immunosuppression that may contribute to the emergence of skin tumors. Immune suppression results from the induction of suppressor T cells, either by damaged Langerhans cells or inflammatory macrophages that enter the skin following UV exposure [10]. Another mechanism may be the release of cytokines such as IL-10, TNF-α, and IL-1α that can suppress the immune system and prevent T-cell mediated responses; these are known to be secreted by keratinocytes after UV damage [11]. In addition, UV irradiation can also convert normal skin chromophores into agents that are immunosuppressive, such as the conversion of *trans*-urocanic acid to *cis*-urocanic acid [12].

Thus, UV radiation plays a dual role in the development of skin cancer, by inducing genetic alterations in keratinocytes leading to their neoplastic transformation and by depressing the normal immune responses in the skin.

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p53 Mutations in Hairless SKH-hr1 Mouse Skin Tumors Induced by a Solar Simulator

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ABSTRACT

In this study, we investigated whether the spectrum of *p53* mutations in skin tumors induced in hairless SKH- hr1 mice by a solar simulator (290-400 nm) are similar to those found in skin tumors induced in C3H mice by UV radiation from unfiltered (250-400 nm) and Kodacel- filtered (290-400 nm) FS40 sunlamps. Analysis of tumor DNA for *p53* mutations revealed that 14 of 16 (87.5%) SkH-hr1 skin tumors induced by the solar simulator contained mutations. Single C ■ T transitions at dipyrimidine sequences located on the nontranscribed DNA strand were the most predominant type of *p53* mutation. Remarkably, 52% of all *p53* mutations in solar simulator-induced SKH-hr1 skin tumors occurred at codon 270, which is also a hotspot in C3H skin tumors induced by unfiltered and Kodacel-filtered FS40 sunlamps. However, T ■ G transversions, which are hallmarks of UVA-induced mutations, were not detected in any of the solar simulator-induced skin tumors analyzed. These results demonstrate that the *p53* mutation spectra seen in solar simulator-induced SKH-hr1 skin tumors are similar to those present in unfiltered and Kodacel-filtered FS40 sunlamp-induced C3H skin

tumors. In addition, our data indicate that the UVA present in solar simulator radiation does not play a role in the induction of ***p53*** mutations that contribute to **skin cancer** development.

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Cancer Research
BECAUSE LIVES DEPEND ON IT

Gene Alterations and Cancer Milestones in Discovery

The last 25 years of research have produced an explosion in our understanding of the nature and causes of cancer. In 1971, a handful of chemicals, viruses, and chromosome abnormalities were associated with cancers, but scientists did not understand what was happening inside the cell to cause cancer.

Today, we know cancer is a genetic disease in which chemicals and viruses are a few of the many factors that cause mutations in our genes. When enough mutations accumulate in a cell, the normal processes inside the cell are disrupted, and tumors can begin to grow.

Cancer occurs when mutations accumulate in two specific kinds of genes: those that encourage cell growth, known as oncogenes, and those that act as brakes on cell growth, called tumor suppressor genes. Mutated or excess copies of oncogenes result in altered or excess protein and too much cell growth. Mutations in tumor suppressor genes result in a protein that is missing or not working that fails to stop abnormal growth. Over 100 of these altered genes have been identified, and the normal cellular roles of many are known.

This timeline highlights many key discoveries in the past 25 years that led to our current understanding of the link between gene alterations and cancer. Many of the human oncogenes mentioned in the timeline (src, ras, abl, myc, sis, erbB, erbA) were first discovered in animal tumor viruses.

1969 Normal cells are found to have genes that suppress the growth of tumors. When a rat tumor cell line was fused with normal cells, the tumor cells were no

longer able to cause tumors in laboratory rats - showing that normal cells have genes that suppress the tumor cell genes.

1970 The first oncogene, now known as the src oncogene, is identified in a chicken tumor virus. The chicken virus, an RNA tumor virus discovered in 1911, was known to cause chicken tumors, but it was not known at the time that a specific **gene** in the virus caused the tumors.

1973 Cancer is linked to DNA exchanges between chromosomes. The chromosomes of patients with chronic myelogenous leukemia (CML) were found to have pieces of chromosome 9 and chromosome 22 exchanged.

1976 Oncogenes are discovered in normal DNA. The src oncogene (see 1970) was found in normal chicken DNA, showing that oncogenes do not have to come from outside the cell via a virus. This experiment suggested that a normal **gene** already present in the cell has the potential of becoming an oncogene.

1978 The Src protein is found to be a member of the protein kinase family of enzymes. This was the first clue to the function of an oncogene. Although the exact function of the Src protein was not known, this family of enzymes was known to be involved in cellular communications.

1979 The first human RNA tumor virus, HTLV-1, is discovered. The virus is associated with adult T-cell leukemia. (About 80 RNA animal tumor viruses from many species - chicken, mouse, rat, cat, baboon - had already been discovered; this was the first human RNA tumor virus.)

1981 Hepatitis B virus is associated with liver cancer.

1981 The first biologically active human tumor oncogene is identified from a human bladder carcinoma cell line.

1982 The 1981 human tumor oncogene is identified as H-ras, similar to an oncogene previously found in rat RNA tumor virus.

1982 DNA analysis shows that the difference between the ras oncogene and ras proto-oncogene (the normal **gene** before it is altered to become an oncogene) lies in a change in a single base (a subunit of DNA).

1982 The myc oncogene is found to be activated in Burkitt's lymphoma, a form of leukemia. This showed the association between cancer and an overproduced oncogene product. In the lymphoma, the oncogene becomes activated when it is transferred from chromosome 8 to chromosome 14.

1982 The **abl** oncogene is found to be activated in leukemia (CML) patients. This showed the association between cancer and an overly active oncogene product. In CML, when the oncogene is transferred from chromosome 9 to chromosome 22, the mutated **Abl** protein was found to be a fusion product - part of **Abl** is fused with another protein, making it much more active in the cell (see 1973).

1982 Several copies of the myc oncogene are found in human leukemia cells. This is the first evidence that an oncogene can become activated by having an excessive number of **gene** copies in a cell.

1983 The sis oncogene product is found to be a mutant form of a known protein, the platelet-derived growth factor (PDGF). This discovery provided the first link between an oncogene and a protein with a known function in the cell.

1984 The erbB oncogene product is discovered to be a truncated version of a protein (the epidermal growth factor receptor) that sits on the surface of certain cells. This discovery showed how a mutation in an oncogene can disrupt the normal function of the protein product. (The mutated ErbB protein was found to lack the part of the receptor that normally binds to molecules outside the cell.)

1985 Researchers discover that proto-oncogenes can function as transcription factors (proteins in the cell nucleus that regulate **gene** activity). The erbA oncogene product was shown to be similar to thyroid hormone receptors that were known transcription factors.

1986 The first tumor suppressor **gene**, Rb1, the retinoblastoma **gene**, is isolated. Genetic studies show that the development of retinoblastoma is due to inactivation of both copies of the Rb **gene**.

1988 An oncogene is associated with apoptosis, or programmed cell death. The Bcl-2 oncogene product, isolated from B-cell lymphoma, is shown to block programmed cell death in B cells.

1989 **p53** is recognized as a tumor suppressor **gene**. Both copies of the **p53 gene** are inactivated in about 50 percent of cancers. (**p53** was originally discovered in 1979 and thought to be an oncogene.)

1990 A rare familial cancer, the Li-Fraumeni Syndrome, is linked to mutations in both copies of the **p53 gene**.

1991 The APC (adenomatous polyposis coli) tumor suppressor **gene**, associated with hereditary colorectal cancer, is isolated.

1993 Several tumor suppressor genes associated with familial cancers are isolated: NF2, associated with acoustic nerve and brain tumors; VHL, associated with benign and malignant tumors in the kidney, retina, central nervous system, pancreas, and adrenal gland; and NTS-1/p16, a cell cycle inhibitor associated with malignant melanoma and pancreatic cancer.

1993 & 1994 Additional tumor suppressor genes associated with familial cancers are isolated: MSH-2 and MLH-1, associated with hereditary nonpolyposis colon cancer (HNPCC), are known to function normally in DNA repair; their mutated forms disrupt DNA repair.

1994 & 1995 Additional genes associated with familial cancer syndromes are

isolated, including two tumor suppressor genes: BRCA1, associated with breast and ovarian cancer, and BRCA2, associated with breast cancer. One oncogene, CDK4, associated with melanoma, was also isolated; this proto-oncogene is a regulator of the cell cycle.

In spite of the unprecedented inroads into our understanding of the molecular basis of cancer, extraordinary challenges remain. Researchers estimate that there are probably a hundred or more genes involved in cancers, in addition to the 100 already identified (about 80 oncogenes and 20 tumor suppressor genes). Also, most cancers involve mutations in several genes, and the patterns of genes that are altered in individual tumors and cancers have yet to be defined.

The hope is that future cancer research will continue to build on the achievements of the past 25 years, and oncogenes and tumor suppressor genes can provide novel targets for the development of anticancer drugs.

The Cancer Information Service provides a nationwide telephone service for cancer patients, and their families, the public, and health care professionals. The toll-free number is 1-800-4-CANCER (1-800-422-6237); services are provided in English and Spanish. People with TTY equipment may call 1-800-332-8615.

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